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Space radiation risks to the central nervous system

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ABSTRACT

Central nervous system (CNS) risks which include during space missions and lifetime risks due to space radiation exposure are of concern for long-term exploration missions to Mars or other destinations. Possible CNS risks during a mission are altered cognitive function, including detriments in short-term memory, reduced motor function, and behavioral changes, which may affect performance and human health. The late CNS risks are possible neurological disorders such as premature aging, and Alzheimer's disease (AD) or other dementia. Radiation safety requirements are intended to prevent all clinically significant acute risks. However the definition of clinically significant CNS risks and their dependences on dose, dose-rate and radiation quality is poorly understood at this time. For late CNS effects such as increased risk of AD, the occurrence of the disease is fatal with mean time from diagnosis of early stage AD to death about 8 years. Therefore if AD risk or other late CNS risks from space radiation occur at mission relevant doses, they would naturally be included in the overall acceptable risk of exposure induced death (REID) probability for space missions. Important progress has been made in understanding CNS risks due to space radiation exposure, however in general the doses used in experimental studies have been much higher than the annual galactic cosmic ray (GCR) dose (~0.1 Gy/y at solar maximum and ~0.2 Gy/y at solar minimum with less than 50% from HZE particles). In this report we summarize recent space radiobiology studies of CNS effects from particle accelerators simulating space radiation using experimental models, and make a critical assessment of their relevance relative to doses and dose-rates to be incurred on a Mars mission. Prospects for understanding dose, dose-rate and radiation quality dependencies of CNS effects and extrapolation to human risk assessments are described.

1. Introduction

Experimental studies at particle accelerators with protons and high charge and energy (HZE) nuclei have suggested that during mission and late risks to the central nervous system (CNS) from galactic cosmic rays (GCR) and solar particle events (SPEs) could be a limitation to human exploration of our solar system (NAS, 1973, 1996; NCRP, 2006; Cucinotta et al., 2009). However, there remains an important scientific challenge of extrapolating observations from these studies to humans and vital need to perform new experiments at space relevant doses and dose-rates to understand the during mission and late CNS risks. Because of the relatively low doses of space missions (<0.5 Gy), the early (during mission) space radiation CNS risks will likely be distinct compared to acute and delayed radiation injury that occur after very high doses of radiation (Tofilon and Fike, 2000). In addition, for during mission CNS risks there are potentially synergistic interactions with other spaceflight factors such as altered circadian rhythm and microgravity. In this review, we first summarize exposures to be encountered on Mars missions which show the maximum annual exposure from GCR to be no more than 0.2 Gy/y with less than 50% from HZE particles. Existing human data on CNS risks at low to moderate doses (<2 Gy) are briefly summarized. Recent studies in CNS radiobiology are then discussed, and recommendations on how to define new exposure conditions for CNS research to ensure their relevance for space conditions are discussed.

Radiation protection both on Earth and in space (NCRP, 1989) is based on principles of risk justification and limitation. For stochastic effects such as cancer, acceptable risks are set with an upper limit of 1 in 33 probability of cancer mortality from occupational exposures (NCRP, 1989, 2000) using the quantity risk of exposure induced death (REID) (Cucinotta et al., 2013a, 2013b; Cucinotta, 2014). This compares with the current estimate of 1 in 270 for loss of crew due to flight failures, while new technology investments expected to reduce this value to 1 in 750 (ASAP, 2010). Dose limits for deterministic effects including risks to the skin,

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blood forming system, and lens are based on avoiding all risk with limits set at estimated doses below a likely threshold for clinically significant effects. Deterministic effects are expected to occur only above a dose threshold after a significant number of cells are damaged within a tissue, and with a severity that increases with dose, including an inverse correlation between dose and latency. The Casarett model of late tissue effects (Rubin and Casarett, 1968; Cox et al., 1983) suggests that significant effects will occur at lower doses, but with increased latency compared to higher doses. Recent debate has considered if cataracts will occur without a dose threshold (ICRP, 2012). The increased incidence of cataracts observed after the low space radiation doses of past space missions (Cucinotta et al., 2001, Chylack et al., 2009; Chylack et al., 2012), where only a small fraction of cells in a tissue are damaged, suggests that new paradigms for deterministic effects should be considered. More extensive considerations may be needed for cognitive changes in the CNS that may occur during flight, which likely involve distinct biological factors compared to other tissues related to changes to synapse plasticity and distinct modes of oxidative damage.

In the past, limiting the risks to the CNS of adults exposed to low to moderate doses of ionizing radiation has not been a concern for occupational radiation exposure. CNS injury that occurs after high doses of radiation used in radiotherapy, including early delayed effects such as demyelination and late delayed effects such as vascular damage and white matter necrosis, are not a concern for spaceflight (Tofilon and Fike, 2000; Hopewell, 1994). However, the HZE particle component of space radiation presents distinct biophysical challenges to cells and tissues compared to terrestrial forms of radiation. Soon after the discovery of cosmic rays, the concern for CNS risks originated with the prediction of the light flash phenomenon from single HZE nuclei traversals of the retina (Tobias, 1952), which was later confirmed by the Apollo astronauts. HZE nuclei are capable of producing a column of heavily damaged cells along their path through tissues, described as a microlesion (NAS, 1973; Todd, 1989), possibly leading to negative impacts on CNS function. In the last decade new hypotheses for mechanisms of HZE damage to the CNS have been described related to the observation of cognitive changes, the impacts by HZE nuclei on neurogenesis, and pathological changes related to Alzheimer's disease and other late effects in experimental studies of the CNS.

Human epidemiology is used as a basis for risk estimation for cancer, acute radiation risks, and cataracts using dose-response models from low LET exposures in humans combined with quality factors or relative biological effectiveness (RBE) factors and dose-rate modifiers determined from experimental models. However, this approach is not viable for estimating CNS risks from space radiation because there is no human data from low LET radiation exposure to develop a quantitative scaling approach for space radiation, and it is likely that HZE particles produce qualitatively different biological damage compared to X-rays or gamma-rays. At doses above a few Gy, detrimental CNS changes occur in humans treated with radiation (such as photons and protons) for cancer. Here treatment doses of 50 Gy or more are typical, which is well above the exposures in space even if a large SPE were to occur. Thus, of the categories of space radiation risks, which includes cancer, CNS, degenerative tissue effects, and acute radiation syndromes, CNS risk assessment will rely most extensively on experimental data with animals for its evidence base, and for the development of risk projection models.

2. CNS exposures in space

Both GCR and SPEs are of concern for CNS risks. The GCR are composed of protons, helium nuclei, and high charge and energy (HZE) nuclei. GCR energies ranging from less than 10 MeV/u to above 10,000 MeV/u with median energies inside tissue of about 1500 MeV/u for HZE components and several hundred MeV for protons and helium nuclei. Secondary particles are produced through nuclear reaction in shielding and tissue, including neutrons, protons, helium nuclei, mesons and gamma-rays. The high energies of GCR lead to practical ranges to 100's of cm of any material, thus precluding radiation shielding as an important mitigation approach to GCR risks on the CNS. For SPEs, the possibility exists for an absorbed dose of over 1 Gy from a SPE if the crew is in a thinly shielded spacecraft or during a spacewalk (Kim et al., 2007; Kim et al., 2009) with the likelihood of a SPEs higher near solar maximum and lowest near solar minimum. The energies of SPE (10's to 100's of MeV), however, do not preclude radiation shielding as a potential countermeasure. Nevertheless, the costs of shielding may be too high to protect against the largest events that have occurred historically (Kim et al., 2009).

Table 1
Comparison of NSCR-2012 model to MSL Rad measurements for average dose-rate and dose equivalent rate on cruise phase to Mars and on Martian surface.

	GCR dose rate (mGy/d)	GCR dose eQUIV rate (mSv/d)
Model Cruise to Mars*	0.445	1.80
Model Mars surface*	0.20	0.72
RAD cruise to Mars (Zeitlin et al., 2013)	0.481 ± 0.08	1.84 ± 0.33
RAD Mars surface (Hassler et al., 2014)	0.205 ± 0.05	0.70 ± 0.17

* NSCR-2012 model predictions (Cucinotta et al., 2013a; Kim et al., 2014).

GCR dose-rates are accurately predicted by the NASA Space Cancer Risk Model (NSCR-2012) (Cucinotta et al., 2013a, 2013b) as shown in previous reports comparing to flight measurements (Cucinotta et al., 2008; Cucinotta et al., 2013a; Zeitlin et al., 2013; Kim et al., 2014). Table 1 shows comparison to the recent measurements on the cruise from Earth to Mars, and Martian surface from the MSL-RAD detector (Zeitlin et al., 2013; Hassler et al., 2014). A high level of agreement between measurements and NSCR-2012 is found. Fig. 1 (Panel A) shows the variation of the GCR dose-rate as predicted by the NSCR-2012 model (Cucinotta et al., 2013a, 2013b). In Fig. 1 (Panel B) the contributions to the annual absorbed dose versus the charge number of the particle for several locations within the human brain are shown for the GCR at solar minimum. It is clear that in interplanetary space annual GCR organ doses will vary from about 0.1 Gy to 0.2 Gy per year for solar maximum to solar minimum, respectively and the HZE contribution to the absorbed doses will be 0.1 Gy/y or less (Cucinotta and Durante, 2006; Cucinotta et al., 2013a, 2013b). Round-trip times to Mars are approximately 1-year, however there are also exposures on the surface of Mars with about half the free space dose-rate (Cucinotta et al., 2007; Hassler et al., 2014). These doses will have lower percent-contributions from HZE particles due to their absorption in the Martian atmosphere and an increased contribution from neutrons (Kim et al., 2014). Unfortunately many reports from CNS space radiobiology confuse reported estimates of absorbed dose with dose equivalent, and use estimates of dose equivalent to determine lower dose ranges for experimental design. Because average quality factors for GCR are ~4, such studies are often considering minimal doses well above the annual GCR doses from HZE particles, while not addressing dose-rate effects.

3. Effects in humans and non-human primates at low to moderate doses

3.1. CNS risks after cancer therapy with radiation

Evidence of the effects of terrestrial forms of ionizing radiation on the CNS has been documented from the patients of